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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,263	03/21/2002	Hermona Soreq	2391-00101	1307

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,263	SOREQ ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-15* is/are pending in the application.

4a) Of the above claim(s) *6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Declaration under 37 CFR § 1.132, submitted 5 November 2004 and 7 February 2005, respectively, have been entered. Claims 3 and 4 are cancelled. No Claims were amended.

Claims 1, 2 and 5 are under examination in the Instant Application.

Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement.

Claims 1, 2 and 5 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for the antibody made against the acetylcholinesterase fragment peptide of SEQ ID NO: 1, to be used for identifying production of the AChE splice variant in the brains of mice, does not enable an antibody made against a variety of possible acetylcholinesterases for *diagnosing central nervous system stress* in animals or humans, or for identifying production of the AChE splice variant in animals other than mice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims. This rejection was made in a previous Office Action (5 January 2004).

The claims recite use of an antibody against a splice variant of acetylcholinesterase called

AChE-R, identifiable by its atypical C-terminal. The claims embrace antibodies made against many or all variants of acetylcholinesterase identified by the presence of the I4 peptide, for use in diagnosing central nervous system (CNS) stress. A dependent claim recites stress "caused by any one of psychological, chemical and physical insult."

The breadth of Claims 1, 2 and 5 is too large since the specification fails to provide any guidance on how to use antibodies against AChE splice variants for the purpose of diagnosing central nervous system stress. Applicants have not demonstrated that they have diagnosed a "central nervous system stress," but instead demonstrated expression of the AChE-R variant in the hippocampi of mice forced to swim in the "confined swim stress" test. AChE-R splice variant expression is also shown by Western blot in glioblastoma samples (Figure 1), labeled as "stressed" or "non-stressed," as well as in mice transfected with the glioblastoma AChE-R splice variant (Figure 2). Similar measurements were made in the cerebral spinal fluid of Alzheimer's disease patients, using an antibody against *alpha-ARP*, a protein with an unknown relationship or correlation to the AChE-R splice variant identified by SEQ ID NO: 1. Although the experiments with human CSF refer to "stressed" versus "non-stressed" humans, it should be kept in mind that stress is defined in a rather circular way in the instant Specification:

"Non-stressed humans" refers to patients in which no enhanced Omnipaque signal was detected by CT brain scan, while "stressed humans" refers to patients in which an enhanced Omnipaque signal was detected by CT brain scan" (Specification, page 20).

The specification does not enable use of the AChE-R antibody to diagnose a "central nervous system (CNS) stress." Since "central nervous system (CNS) stress" is poorly defined in the instant Specification, and may encompass a variety of neurological disorders (such as stroke,

drug overdose and cancer, for example), and since the instant Specification is enabling only for identifying production of AChE-R in mice, a more specific phrase is needed to describe the condition the Applicant is intending to diagnose. The Specification describes use of antibodies made to SEQ ID NO: 1 to identify production of the AChE-R splice variant in mice hippocampi after the mice were subjected to a swim stress test. Aside from identification of the AChE-R splice variant in mice, diagnosis of a "central nervous system (CNS) stress", as claimed, is not adequately disclosed. The Specification has not provided a nexus between Ache-R (variant) production and a disease condition in need of diagnosis. It is not known, nor can it be inferred from the Specification, what the patient population is or why it would be necessary to diagnose the type of stress that results in this splice variant.

In summary, the specification does not provide a description of a repeatable process of using antibodies to acetylcholinesterase splice variants for the purpose of diagnosing "central nervous system stress." Nor can antibodies to AChE-R be used to identify changes in the brain of humans or animals other than mice subjected to standard tests that provoke anxiety or fear. Furthermore, there is no evidence that the AChE-R splice variant is made in humans or other animals besides mice, except for its expression in certain cancers (Karpel, et al, 1994, Accession No. S71129).

The Declaration of Dr. Soreq, filed under 37 CFR 1.132 (5 November 2004), is insufficient to overcome the rejection of claims 1, 2 and 5 based upon 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

The Inventor, Dr. Soreq, discusses examples of several physical and psychological stressors in humans, but provides no information about a physiological nexus common to all:

"Stress is understood as a physiological (and psychological, when referring specifically to humans) state, which is triggered in response to altered internal and environmental conditions such as, for example, exposure to chemical stressors (e.g. poisonous organophosphate insecticides), immunological agents (e.g. bacterial lipopolysaccharide) or experiencing a terror attack. This "physiological state" is the organism's response to said triggering factors, and it might reveal itself in the form of transiently enhanced release of acetylcholine (ACh), erratic behavior following circadian light/dark shift, progressive muscle fatigue and degeneration of neuromuscular junctions, progressive failure of learning and memory, and development of neuropathologies (Soreq, H. et al. (2004) [additional references omitted] In sum, there are a series of manifestations that together are described by a word "stress". These manifestations, or responses, are primarily (and ultimately) regulated by the central nervous system (CNS) and thus, are also denominated CNS stress" (Declaration, page 3).

While it is true that the Inventors discovered a variant Ache in mice subjected to physical/strongly-emotional stress (the forced-swim test), it is still not clear if the mouse antibody will reveal a variant Ache in humans and exactly what disease such an antibody can "diagnose." In addition such stresses are not commensurate is scope with the conditions the Specification associates with stress, including cancer, drug overdose, and stroke.

Due to the large quantity of experimentation required to determine how to: use antibodies against splice variants of acetylcholinesterase to diagnose a "central nervous system (CNS) stress," the lack of direction or guidance in the specification regarding the conditions that can be diagnosed using such antibodies, the lack of working examples whereby "central nervous system (CNS) stress[es]" are identified or diagnosed, and the state of the art showing the unpredictability of making antibodies against variant antigens -undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1, 2 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite

for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 5 are rendered indefinite because of the phrase "central nervous system (CNS) stress," which is a conditional term that is poorly defined in the Specification (see the discussion of Enablement, above). "Stress" may refer to production of cortisol due to fear or anxiety, which has been shown to cause CNS changes (Magariños, et al, 1997, Proc. Natl. Acad. Sci., 94: 14002-14008) or may refer to trauma or a physiologically-demanding situation. The phrase "central nervous system" as related to stress encompasses a variety of diagnosable and non-diagnosable conditions, such as stroke and cancer.

This rejection can be overcome by supplying specific states or clinical conditions, supported by the specification, which can be diagnosed using antibodies against SEQ ID NO: 1, or by removing language referring to "central nervous system stress."

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion: Claims 1, 2 and 5 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elyaber C. Kemmerer

SLW
10 May 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER